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Dated: November 24, 2003 Signature: Monica L. Thomas
(Monica L. Thomas)

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12/11/03

Docket No.: HO-P01952US0
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Julie A. Bearcroft, et al.

Application No.: 09/517,981 Group Art Unit: 3738

Filed: March 3, 2000 Examiner: B. Pellegrino

For: SHAPED PARTICLE AND COMPOSITION FOR BONE DEFICIENCY AND METHOD OF MAKING THE PARTICLE

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DECLARATION UNDER 37 CFR §1.132

Dear Sir:

I, Michael B. Cooper, do hereby depose and say as follows:

1. I am a United States citizen residing at 5665 Dunwoody Ave., TN, USA.
2. I am an employee of the assignee of the above-referenced patent application, I am an inventor of said application, and I have read the contents of said application.
3. I am a Manager of Research Projects at Smith + Nephew, Inc. I am skilled in the area of bone substitute methods and compositions. A resume describing my experience is attached to this declaration.

Issues under 35 U.S.C. § 102(b)

Claims 1-4, 9, 10, 20-22, 26, 64, 67-70, and 73-78 are rejected under 35 U.S.C. § 102(b).

Sheppard does not teach all elements of any claim in our present invention. Specifically, in Sheppard on Page 2, lines 6-25 there is description of experiments regarding packing densities of spheres. However, *spheres have no extremities, and the particular spheres described in this section also have no extremities*. It is extremely unreasonable to assert that anyone of skill in the art would correlate these spheres lacking extremities and mentioned in the background section of Sheppard with the particles having square cross-sectional shaped extremities depicted in FIGS. 2, 5, and 6. Sheppard clearly does not teach a toy jack-shaped article having extremities such as the one of our present invention. No skilled artisan would read the background discussion regarding spheres and packing thereof and believe that the

particle of Sheppard FIG. 2 and particles of Sheppard FIGS. 5 and 6 having extremities, planar-sided in nature, would have circular cross-sectional embodiments.

Issues under 35 U.S.C. § 103(a)

Claims 2, 3, 5-8 10-16, 22, 65, 68, 71-74, and 78 remain rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over U.S. Patent No. 5,676,700 ("Black") alone and in combination with other references.

The present invention is not obvious in view of Black for multiple reasons. It can not be understated that the matter of design choice for the shape of a bone graft substitute is not an obvious or predictable one because it is unknown how and why a particular shape facilitates bone ingrowth from the respective osteoblast cells. As discussed in the articles submitted herewith, it is a matter of experimentation to determine the utility of a particular shape, because the successful design shape is not obvious, predictable, or suggestable by another shape.

For example, in several references from the laboratory of Ugo Ripamonti (Ripamonti *et al.,* 1992; Ripamonti, 1994; and Magan *et al.,* 1996) the issue of design shape for induction of bone ingrowth is addressed. Ripamonti *et al.* (1992) note that the geometry of a platform for bone induction, such as a substratum generated from the collagenous extracellular matrix of bone obtained after dissociative extraction, had a profound influence on bone induction. In an art-approved rat pectoralis fascia model, implants of different geometry were inserted. As stated in the Discussion on page 210 of the article:

> The dramatic difference observed between substrata of granular and disc configuration underscores the importance of geometry in bone formation by induction. The critical role of geometry of the substratum in the regulation of cell growth and in endochondral bone differentiation has been reported previously with collagenous matrix, indicating that the endochondral sequence can be greatly altered by the shape of the inductive substratum....

Thus, given that it was known that geometry is a factor to be considered, the authors proceeded to test different shapes for the experiments in this article. This emphasizes the uncertainty in the art regarding shape designs amenable for bone growth and indicates it is

not obvious or predictable which shape would work. If it were obvious, the different shapes would not be tested or need to be tested.

Ripamonti (1994) extends this experiment into an art-approved baboon model relating to reconstructive craniofacial surgery. Substrata of different configurations, rod blocks of hydroxyapatite or granular hydroxyapatite, were implanted onto anterior peritoneal fascia. Substantially no bone formation occurred with the granular hydroxyapatite, which confirms the importance of geometry of the substratum in bone differentiation. Again, the authors were unclear which design would work well, or even better than the other, and therefore tested the two configurations in experiments described therein.

Magan *et al.* (1996) further expands on these findings by testing hydroxyapaptite disks prepared from either longitudinally-cut coral or transversally-cut coral, which results in two distinct implant geometries. Greater amounts of bone formed in porous hydroxyapatites cut longitudinally compared to those cut transversally, affirming that the geometric configuration of the porous hydroxyapatite influences bone ingrowth and osteogenesis. Thus, these references by Ripamonti and colleagues, the skilled artisans, prove that there is not an obvious matter of design choice concerning platforms or strata for bone growth. It is clearly not predictable which design would work, since the researchers are required to experiment with the designs to determine the most suitable one.

By about the time of filing of the present invention, the concept of geometrical shape affecting osteoblast/material interactions was well established enough to discuss in a review (Anselme, 2000). The extent to which this issue has been addressed by these researchers underscores the lack of knowledge and uncertainty in the art related to shape/bone ingrowth issues. Osteoblasts are attracted to different types of surfaces, and it is not predictable which surface shapes will work well. Therefore, it cannot be an obvious matter of design choice if the skilled artisans themselves test different designs to determine suitability.

Even in related medical arts, it is unknown and therefore experimentally tested whether or not different shapes can facilitate induction of cartilage formation. In Kim *et al.* (1993), synthetic polymer scaffolds in the shape of a triangle, rectangle, cross, or cylinder were tested for the ability to create cartilage in these pre-determined shapes using cell transplantation on appropriate polymer templates. Thus, similar to the uncertain relationship between scaffold shape and induction of bone, the induction of cartilage in the presence of different-shaped

scaffolds has an uncertain result, indicating the design of the shape to use for this application is not obvious.

Furthermore, given that the shaped particles of the present invention are designed to reflect both interlocking of adjacent particles and the porosity useful for a bone treatment, specifically for ingrowth of bone, it is not obvious which cross-sectional shape or shapes would impart both of such advantages, and an infinite number of cross-sectional shapes could be tested in determining one that is useful for both interlocking and porosity, similar to different shapes being tested in the submitted references.

Not only can a circular cross-section **not** be obvious in view of an oval, given the dearth of knowledge and the unpredictability in the art, but a skilled artisan from reading Black would likely refrain from considering a circular cross-section design. The Black reference espouses the advantages of having an oval cross-sectional configuration (col. 3, lines 33-38). Because of this teaching and the unpredictability of useful shapes in the art, a skilled artisan in this field would not necessarily presume a circular cross-section would have the same advantage and, furthermore, would likely avoid the labor and expense to perfect its design and manufacture, given the acknowledged advantage of the oval cross-section.

Black states (col. 3, lines 23-42):

> The tightly meshed array 42 of interlocked structural elements 10 establishes a structural matrix of sound mechanical cohesive characteristics for attaining desirable mechanical properties, while providing an osteoconductive or osteoinductive matrix for the ingrowth of natural bone. Thus, the interengaged structural elements 10 are meshed tightly enough and are interlocked to provide a structural matrix which tends to resist shear stress in essentially all directions within the array 42, while the nature of the material of the structural elements 10 allows for the ingrowth of natural bone. The oval cross-sectional configuration of the posts 12, and the tapering of the posts 12 along the length L thereof, enhance the ability of the posts 12 to enter the inter-post spaces 16 and attain meshing and interlocking of the structural elements 10 in the desired tight relationship. The mechanical strength of the matrix thus provided by the array 42 is sufficient to enable load-bearing, even upon initial implant of the femoral implant 32, whether utilized alone to fill a void such as cavity 30, or in combination with autologous bone or autologous blood.

Thus, Black teaches that its particles have similar advantages to those demonstrated by our particles. If a skilled artisan is taught by Black that a particle with an oval cross-section has the advantage of providing both porosity and an interlocking shape, then why would a skilled artisan presume the same would be provided by a shape lacking the contour of an oval (*e.g.* not having two longer "sides" of its contour), particularly when Black asserts: "[the] oval cross-sectional configuration of the posts...enhance[s] the ability of the posts...to enter the inter-post spaces...and attain meshing and interlocking"?

Moreover, the circular cross-section of the extremities of the particle are definitely not an obvious matter of design choice, particularly given their inherent functional differences. That is, although the cross-sectional area has proportionately the same forces in any direction across a circular cross-section, an oval cross-section has disproportionate forces depending on the direction across the cross-section. For example, the forces across the different amounts of material (depending on the direction) of the cross-section in the oval-based arm provides weaker points in terms of tensile strength and so forth. *These inherent functional differences mean that the design of the oval is not interchangeable with the design of the circle. The substitution of a circle for an oval cross-section is not a trivial substitution, and in the design of the particles of the present invention we have discovered that the circular cross-sectional properties are critical to how it functions. It would not be a mere design choice to exchange circle for oval.*

In summary, I hereby state that there is no obvious design choice to any bone graft substitute because of the unpredictability of osteoblast/bone ingrowth preferences, as demonstrated by those of skill in the art ***testing*** this matter. If the shape was obvious, it would not need to be tested. Also, the functional difference between oval and circular cross-sections render the two shapes non-interchangeable, which means that one is not an obvious choice in light of another. Finally, Black teaches away from our invention by stating the advantage of having an oval cross-section. Therefore, the rejected claims in the present invention ***can not*** be obvious in view of Black or any combination with other references thereof.

4. I hereby declare that all statements made herein on my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 11-13-03

Michael B. Cooper